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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,385	10/27/2003	Brian J. Stockman	6283.N DV1	5758

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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 06/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,385	STOCKMAN ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/1/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/1/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 18-30 are pending and examined.

Priority

2. This application, filed 10/27/2003, states that it is a Divisional of 09/677,107; filed 9/29/2000; which claims benefit of 60/156,816, filed 9/29/1999; 60/161,682, filed 10/26/1999; and 60/192,685, filed 3/28/2000.

3. Applicant is respectfully requested to update the status of parent application 09/677,107, now US Patent No. 6,677,160.

Information Disclosure Statement

4. The information disclosure statement, filed 3/1/2004, fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the citation to Bruker does not provide a publication year. It has been placed in the application file, but the information referred to therein in regard to the citation to Bruker, has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement,

including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections - 35 USC § 112, First Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 29 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether undue experiment is necessitated. These factors can include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the relative skill of those in the art;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1 and 2) The breadth of the claims and the nature of the invention: The claims are drawn very broadly to "identifying a compound that binds to a target molecule" using a particular NMR technique. However, claim 29 recites that "dissociation constant of a test compound that binds to the target molecule is at least about 100 μM".

(3 and 5) The state of the prior art and the level of predictability in the art: NMR was known in the art at the time of filing (see Hajduk et al., cited below); however, the specification provides no guidance or direction to permit one of skill in the art to devise steps for determining, in advance, whether *any* test compound of a library has a dissociation constant of "at least about 100 μM" with *any* protein target molecule. The structures of possible compounds and targets are sufficiently diverse and one of skill in the art would not be able to predict their structure. One of skill could not guess, *a priori*, how to carry out the claimed method where the "dissociation constant of a test compound that binds to the target molecule is at least about 100 μM" in the absence of any guidance as to the chemical structures of these entities or the steps of the method without undue experimentation. Applicant's claim represent only an invitation to experiment.

(4) The level of one or ordinary skill: The level of skill would be high, most likely at the Ph.D. level. However, such persons of ordinary skill in this art, *given its unpredictability*, would have to engage in undue (non-routine) experimentation to carry out the invention as claimed.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants have provided no working examples of the claimed

method. It appears that the claims omit matter that is essential to the invention. Claim 29 discloses no information on the structures of the compound or target or how the dissociation constant is to be determined. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976) regarding omission of essential matter; *see, also* MPEP 2164.08(c).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: Therefore, the instant specification does not provide to one skilled in the art a reasonable amount of guidance with respect to the direction in which the experimentation should proceed in carrying out the claimed invention. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to tech those of skill in the art how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Thus, it is deemed that undue experimentation would be required to make and use the invention as claimed.

Claim Rejections - 35 USC § 112, Second Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

8. Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 recites that the "dissociation constant of a test compound that binds to the target molecule is at least about 100 μM". However, it is completely unclear as to applicants' intent as there is not a structure present for either the target or the compound and no method steps for determining the dissociation constant. Therefore, the claims are incomplete and unclear.

Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as appearing to be incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: identifying a compound from the library that binds to the target molecule with a dissociation constant of at least about 100 μM.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 18-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Hajduk et al.**, J. Am Chem. Soc. 1997, 119, pp. 12257-12261 (IDS entered 3/1/2004); and in view of **Keifer**, Drugs of the Future 1998, Vol. 23, No. 3, pp. 301-317 (IDS entered 3/1/2004).

The claims are drawn to a method of identifying a compound that binds to a target molecule, the method comprising: providing a plurality of mixtures of test compounds, each mixture being in a sample reservoir; introducing a target molecule into each of the sample reservoirs to provide a plurality of test samples; providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; transferring each test sample from the sample reservoir into the flow-injection probe; collecting a relaxation-edited nuclear magnetic resonance spectrum on each test sample in each sample reservoir; and comparing the spectra of each test sample to the spectra taken under the same conditions in the absence of the target molecule to identify test compounds that bind to the target molecule; wherein the concentration of target molecule and each test compound in each sample reservoir is no greater than about 100 μM; and variations thereof.

Hajduk et al., J. Am Chem. Soc. 1997, 119, pp. 12257-12261, throughout the publication and abstract, disclose one-dimensional ^{1}H NMR techniques for screening

libraries of compounds for binding to a macromolecule that is a protein, particularly the FK506 binding protein, ("FKBP"), by relaxation-edited detection of ligand binding; which reads on the instantly claimed method of identifying a compound that binds to a target molecule, the method comprising: providing a plurality of mixtures of test compounds, each mixture being in a sample reservoir; introducing a target molecule into each of the sample reservoirs to provide a plurality of test samples; and collecting a relaxation-edited nuclear magnetic resonance spectrum, as in *claims 18, 23, 24, 30*.

Hajduk et al., at p. 12258, para 2-p. 12259, para 2, teach relaxation-edited 1-dimension NMR detection of ligand binding to mixtures comprising a library of nine compounds containing 2-phenylimidazole, which binds to FKBP with an affinity of 200 μM, (and which absent evidence to the contrary, reads on a dissociation constant of a test compound that binds to the target molecule of at least about 100 μM, as in *claim 29*) and eight compounds that do not bind to the protein, (and wherein these compounds read on test compounds having molecular weights no greater than about 350 grams/mole, as in *claims 22, 25, 26*). Hajduk teach obtaining a relaxation-edited spectrum of the test compounds in the absence of FKBP, then obtaining relaxation-edited spectra of FKBP alone and of the test compounds in the presence of FKBP and subtraction to produce a spectrum (Figure 2B) and to identify, from the difference spectrum (Figure 2c), compounds that bind to FKBP; which reads on collecting a relaxation-edited nuclear magnetic resonance spectrum on each test sample in each sample reservoir; and comparing the spectra of each test sample to the spectra taken

under the same conditions in the absence of the target molecule to identify test compounds that bind to the target molecule, as in *claim 18*.

Hajduk et al., at p. 12260, para 2-3, teach samples containing, e.g., 50 μM FKBP protein and 50 μM of each ligand, (which reads on the concentration of the target molecule and each test compound in the sample reservoir being no greater than about 50 μM, as in *claim 28*) or 100 μM stromelysin and 100 μM of each ligand, in a 95% D_2O buffered solution, (wherein the particular compounds taught have, absent evidence to the contrary, solubility in deuterated water of at least about 1mM at room temperature, as in *claim 21*; and wherein the ratio of target molecule to each test compound in the sample reservoir is about 1:1, as in *claim 27*); which reads on the claimed method wherein the concentration of target molecule and each test compound in each sample reservoir is no greater than about 100 μM, as in *claim 18*.

Hajduk et al., does not disclose methods for identifying compounds comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe.

Keifer, Drugs of the Future 1998, Vol. 23, No. 3, pp. 301-317, throughout the publication, and especially at p. 308, para 5-p. 313, para 3, teaches probes specifically designed to handle small-volumes (less than 40 microliters), and particularly at p. 311, para 5-p. 312, para 1, teach flow injection NMR by transferring an aliquot of sample from a microtiter plate (also, Keifer, at p. 310, para 2, teaches microtiter plate-based NMR that contemplates 96-well microtiter plates; and as in *claims 19, 20*); which reads

on providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe, as in *claim 18.*

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used methods for identifying compounds comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe; and to use multiwell and 96-well microtiter plates in such methods.

One of ordinary skill in the art would have been motivated to make and use methods for identifying compounds comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe, because Kiefer teaches transferring test samples from microtiter plates by flow-injection probe to for NMR analysis, is desirable in order to acquire high-quality NMR spectra in a rapid and automated fashion (e.g., Kiefer at p. 310, para 2, pp. 312-313, bridging paragraph), and particularly, to screen combinatorial chemistry compounds or mixtures of compounds in order to speed up the entire drug discovery process (e.g., Kiefer at p. 301, para 1).

One of ordinary skill in the art would have had a reasonable expectation of success in using methods comprising providing a nuclear magnetic resonance spectrometer equipped with a flow-injection probe; and transferring each test sample from the sample reservoir into the flow-injection probe, because Kiefer teaches such

flow-injection probes were commercially available; (Kiefer at p. 308, para 3, citing the "Nanoprobe" from Varian).

Conclusion

11. Claims 18-30 are rejected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark L. Shibuya
Examiner
Art Unit 1639